Outcome comparison between surgically treated brain arteriovenous malformation hemorrhage and spontaneous intracerebral hemorrhage

Sun, Wenhua ; German, Menno R ; Sebök, Martina ; Fierstra, Jorn ; Kulcsar, Zsolt ; Keller, Annika ; Regli, Luca

Abstract: BACKGROUND Case fatality and poor outcome rates are different between brain arteriovenous malformation associated intracerebral hemorrhage (bAVM-ICH) and spontaneous intracerebral hemorrhage (SICH). These outcome rates, however, have never been compared in patients who need neurosurgical evacuation of the intracerebral hemorrhage (ICH). OBJECTIVE To compare the short- and long-term functional outcome between surgically treated patients with bAVM-ICH and SICH. METHODS We collected data from surgically treated ICH patients at the department of neurosurgery, University hospital Zurich, from January 2015 to July 2018. We performed logistic regression analysis to compare the functional outcome between groups, adjusting for demographics, admission characteristics and stroke risk factors. RESULTS A total of 26 bAVM-ICH and 115 SICH patients were included in the final analysis. Patients with bAVM-ICH were younger and less likely to have hypertension without significant differences in ICH volume, hematoma location, intraventricular hemorrhage and other stroke risk factors. A significantly better functional outcome rate was seen in bAVM-ICH patients at short- and long-term follow-up. These differences remained significant after adjusting for confounders. CONCLUSIONS Patients with a bAVM who need surgical evacuation of an ICH have a more favorable outcome than surgically treated patients with spontaneous ICH, even after correction for confounding factors, such as younger age and less premorbid hypertension.

DOI: https://doi.org/10.1016/j.wneu.2020.04.170

Outcome Comparison Between Surgically Treated Brain Arteriovenous Malformation Hemorrhage and Spontaneous Intracerebral Hemorrhage

Wenhua Sun[1,2], Menno R. Germans[1,2], Martina Sebök[1,2], Jorn Fierstra[1,2], Zsolt Kulcsar[2,3], Annika Keller[1,2], Luca Regli[1,2]

■ BACKGROUND: **Case fatality and poor outcome rates are different between brain arteriovenous malformation–associated intracerebral hemorrhage (bAVM-ICH) and spontaneous intracerebral hemorrhage (SICH). These outcome rates, however, have never been compared in patients who need neurosurgical evacuation of the intracerebral hemorrhage (ICH).**

■ OBJECTIVE: **To compare the short- and long-term functional outcome between surgically treated patients with bAVM-ICH and SICH.**

■ METHODS: **We collected data from surgically treated ICH patients at the Department of Neurosurgery, University Hospital Zurich, from January 2015 to July 2018. We performed logistic regression analysis to compare the functional outcome between groups, adjusting for demographics, admission characteristics, and stroke risk factors.**

■ RESULTS: **A total of 26 bAVM-ICH and 115 SICH patients were included in the final analysis. Patients with bAVM-ICH were younger and less likely to have hypertension without significant differences in ICH volume, hematoma location, intraventricular hemorrhage, and other stroke risk factors. A significantly better functional outcome rate was seen in bAVM-ICH patients at short- and long-term follow-up. These differences remained significant after adjusting for confounders.**

■ CONCLUSIONS: **patients with a bAVM who need surgical evacuation of an ICH have a more favorable outcome than surgically treated patients with spontaneous ICH, even after correction for confounding factors, such as younger age and less premorbid hypertension.**

INTRODUCTION

Intracerebral hemorrhage (ICH) is a devastating disease that can lead to high mortality and morbidity. The incidence of ICH is approximately 25 per 100,000 person-years, and it has a mortality of 40% within 1 month of presentation. ICH can be classified as primary or secondary, depending on the etiology of hemorrhage. Primary ICH is most commonly caused by chronic arterial hypertension, whereas secondary ICHs are caused by underlying lesions, such as aneurysms, vascular malformations, or tumors.[1]

A brain arteriovenous malformation (bAVM) is a vascular malformation, which most often causes clinically significant ICH. Although the incidence of bAVM is rare, about 1.12–1.42 per 100,000 person-years, bAVM-associated ICH (bAVM-ICH) has a high impact on the socioeconomic and health care system.[2-5] The annual risk of bAVM-ICH is approximately 2.3%, which increases to a rate of 4.8% after a previous hemorrhage.[6-8] Reported case fatality and poor outcome rates after bAVM-ICH range between 5% and 25% and 10% and 30%, respectively.[3,9-11] This is lower than reported outcomes after spontaneous ICH (SICH), with a mortality rate of 35%–52% in 30 days and 15%–30% independent functional outcome after 1 year.[3,12-17] Recently, the arteriovenous malformation–related intracerebral hemorrhage score was externally validated and showed better performance in predicting clinical outcome when compared with the ICH score.[18] As such,

Key words
- Arteriovenous malformation
- Cerebral hemorrhage
- Outcome

Abbreviations and Acronyms
bAVM: Brain arteriovenous malformation
GCS: Glasgow Coma Scale
ICH: Intracerebral hemorrhage
mRS: Modified Rankin Scale
SICH: Spontaneous intracranial hemorrhage

From the [1]Department of Neurosurgery, [2]Clinical Neuroscience Center, and [3]Department of Neuroradiology, University Hospital Zurich, Zurich, Switzerland

To whom correspondence should be addressed: Menno R. Germans, M.D., Ph.D. [E-mail: Menno.Germans@usz.ch]

Wenhua Sun and Menno R. Germans contributed equally to the manuscript.

Citation: World Neurosurg. (2020) 139:e807-e811.
https://doi.org/10.1016/j.wneu.2020.04.170

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

treatment and management decisions, as well as providing information about the prognosis after bAVM-ICH, should probably not be based on the results from SICH.

There have been some studies on comparison of morbidity and mortality of bAVM-ICH and SICH and showed that patients with bAVM-ICH have a more favorable outcome than patients with SICH from other causes, independent of patient age and other known predictors of ICH outcome.[3,5] These studies included all various causes of ICH including intracranial aneurysms and the patients in both good and poor clinical admission status.[5,19] However, patients who need surgical evacuation of their ICH are generally in worse clinical condition at admission, which has influenced the clinical outcome. No studies that directly compared the clinical outcome of surgically treated bAVM-ICH with surgically treated SICH were found. We aimed to investigate whether surgically treated patients with bAVM-ICH fare better than SICH patients regarding short- and long-term functional outcomes.

METHODS

Study Design and Data Collection

We performed a retrospective analysis of prospectively collected patient data of patients who underwent semiemergent (within 1 week after diagnosis) neurosurgical evacuation of their ICH at the department of neurosurgery, University Hospital Zurich from January 2015 to July 2018. Patients younger than 18 years and patients with ICH due to traumatic brain injury or cerebrovascular diseases other than bAVM, such as a ruptured intracranial aneurysm, were excluded.

Baseline data consisted of patient characteristics, hematoma parameters, and outcome variables, according to the review article of van Beijnum et al.[3] Patient characteristics included age, sex, Glasgow Coma Scale (GCS), and systolic and diastolic blood pressure at admission. GCS was divided into 3 groups according to arteriovenous malformation–related intracerebral hemorrhage score.[20] Hematoma parameters included location (cortical vs. deep vs. infratentorial), side and size (measured by the ABC/2 method in native brain CT), and presence of intraventricular hemorrhage (IVH).[21] Outcome variables included case fatality and modified Rankin Scale (mRS, assessed by trained physicians) at 6 weeks, 6 months, and 12 months after treatment. A mRS of $\geq$3 was defined as a poor outcome.

Missing data were retrospectively collected from our hospital information system and telephone interviews with the patient or general practitioner. Ethical approval for this study was obtained from the local committee (BASEC number: PB_2017-00093). Informed consent for collecting data for scientific purposes was retrieved through a general consent form, which patients have signed.

Statistical Analysis

The differences in baseline characteristics between the 2 groups were evaluated with Pearson χ^2 test for categorical variables. Continuous variables were compared using parametric statistics when data showed normal distribution and nonparametric statistics when they did not. We compared outcomes using odds ratios (ORs) with 95% confidence intervals (CIs) at 6 weeks and 6 and 12 months after surgery. The differences were considered significant at a P value of < 0.05.

Multivariate logistic regression analysis was performed to evaluate the association between bAVM-ICH and SICH outcomes, with a backward elimination procedure to identify significant confounders. Cutoff values of $P < 0.1$ were used to select the initial set of variables to be included in the initial multivariable model. All statistical analyses were performed with the SPSS statistical software package (IBM SPSS Statistics, version 25).

RESULTS

Baseline Characteristics

In total, 31 bAVM-ICH and 115 SICH patients were extracted from the database. Five bAVM-ICH patients were excluded since they had their surgical treatment more than 1 week after hemorrhage. One SICH patient was lost to follow-up after the 6-weeks' outcome assessment due to emigration and is therefore not included in the 6-months' and 12-months' outcome analysis. The final analysis included 26 bAVM-ICH and 115 SICH patients.

Baseline characteristics are shown in **Table 1**.

Patients with bAVM-ICH were significantly younger (45.5 ± 17.9 vs. 61.6 ± 14.3 years, $P < 0.001$) and less likely to have premorbid hypertension (32.3% vs. 54.8%, $P = 0.026$) compared with SICH patients. There were no significant differences in sex, ICH volume, hematoma location, intraventricular hemorrhage, and other stroke risk factors, such as diabetes mellitus and hyperlipidemia between studied groups.

Functional Outcome and Case Fatality

Table 2 and **Figure 1** present the results of the outcome analysis.

Multivariate analysis was done including the following parameters: age, side, hypertension, and diabetes mellitus. The proportion of SICH patients who were dead or dependent (mRS $\geq$ 3) was significantly higher than bAVM-ICH patients at short- and long-term follow-up. After stratified analysis, the rate of death or dependence remained significantly higher in SICH patients at all follow-up timepoints. There was no difference in case fatality between groups at any follow-up timepoint (**Table 3**).

DISCUSSION

In our study, we found that patients with bAVM-ICH showed better functional outcome compared with SICH patients at short-term (6 weeks) and long-term (6 and 12 months) follow-up. We concluded that bAVM patients who need semiemergent surgical evacuation of their ICH have a better prognosis than surgically treated patients with SICH. Our data suggest that treatment and management decisions, as well as information about the prognosis after bAVM-ICH, should not be based on results of SICH research.

Our study consolidated findings from previous studies that have found a better outcome after bAVM-ICH compared with SICH.[2-5] Our study, however, only included ICH patients who needed surgical evacuation of the ICH, indicating patients in a more severe clinical condition. This is reflected in the worse GCS at

Table 1. Baseline Characteristics of Brain Arteriovenous Malformation-Associated Intracerebral Hemorrhage and Spontaneous Intracerebral Hemorrhage Patients

	bAVM-ICH (n = 26)	SICH (n = 115)	*P* Value
Female gender	11 (42.3)	54 (47.0)	0.828
Age, years (SD)	46.3 ± 17.7	61.6 ± 14.3	<0.001
Side of hematoma (right)	12 (46.2)	70 (60.9)	0.059
History of hypertension	8 (30.8)	63 (54.8)	0.027
Diabetes mellitus	4 (15.4)	35 (30.4)	0.121
Hyperlipidemia	3 (11.5)	33 (28.7)	0.070
Admission GCS			0.259
3–4	10 (38.5)	38 (33.0)	0.767
5–12	14 (53.8)	52 (45.2)	0.563
13–15	2 (7.7)	25 (21.7)	0.171
Admission SBP, mm Hg (SD)	159.8 ± 26.2	153.4 ± 28.6	0.243
Admission DBP, mm Hg (SD)	89.3 ± 25.4	87.82 ± 18.9	0.760
Hematoma location			
Supratentorial	22 (87.1)	88 (76.5)	0.173
Cortical	11 (42.3)	60 (52.2)	0.303
Deep	11 (42.3)	28 (24.3)	0.489
Infratentorial	4 (15.4)	27 (23.5)	0.108
ICH volume >30 cm^3	4 (15.4)	19 (16.5)	0.173
Intraventricular hemorrhage	7 (26.9)	25 (21.7)	0.569

All parameters are presented in numbers with percentages between brackets, unless otherwise stated.
bAVM-ICH, brain arteriovenous malformation–associated intracerebral hemorrhage; SICH, spontaneous intracerebral hemorrhage; SD, standard deviation; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure.

admission in our study as compared with the study of van Beijnum et al[3] (median GCS 8 vs. 15).

Patients with bAVM-ICH are younger than SICH patients and bear fewer risk factors, which can affect outcome after ICH, such as hypertension and diabetes mellitus. Nevertheless, even after adjusting for those confounders the patients with bAVM-ICH remained having a more favorable functional outcome.[22-24] One reason for a better prognosis in bAVM patients is that the malformation mostly ruptures within the nidus itself or in the venous side of malformation, leading to a bleeding with lower pressure instead of acute arterial hemorrhage due to hypertension.[5,22-24] Secondly, a significant part, or even the complete, bAVM is located in a sulcus, leading to a sulcal hemorrhage with less damage of the brain parenchyma than SICH, except for the

Table 2. Poor Outcome (Modified Rankin Scale ≥3) in Brain Arteriovenous Malformation–Associated Intracerebral Hemorrhage and Spontaneous Intracerebral Hemorrhage

Interval	bAVM-ICH (n = 26)	SICH* (n = 115)	OR (95% CI)	Adjusted OR† (95% CI)
6 weeks	19 (73.1)	107 (93.0)	0.20 (0.07–0.63)	0.28 (0.08–0.96)
6 months	16 (61.5)	93 (81.5)	0.36 (0.14–0.91)	0.35 (0.13–0.96)
12 months	14 (53.8)	87 (76.3)	0.36 (0.15–0.88)	0.36 (0.14–0.93)

All parameters are presented in numbers with percentages between brackets, unless otherwise stated.
bAVM-ICH, brain arteriovenous malformation–associated intracerebral hemorrhage; ICH, intracerebral hemorrhage; SICH, spontaneous intracerebral hemorrhage; OR, odds ratio; CI, confidence interval.
*1 patient lost follow-up after 6 weeks post surgery.
†Adjust for age, side of hematoma, history of hypertension, hyperlipidemia.

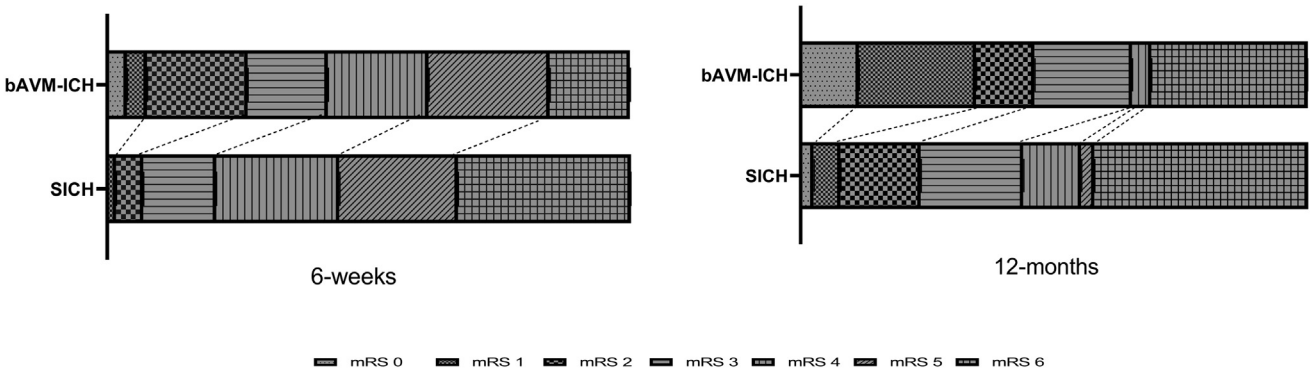

Figure 1. Comparison of modified Rankin scale of patients with brain arteriovenous malformation–related intracerebral hemorrhage (bAVM-ICH) and spontaneous intracerebral hemorrhage (SICH) at 6 weeks and 12 months.

compressive effect of the hematoma itself. Another reason might be the higher proportion of infratentorial hemorrhages in the SICH group, which is associated with a worse clinical outcome. Other studies regarding this topic have shown results with more favorable rates for bAVM-ICH patients at discharge or 1 month after hemorrhage.[3,5] The difference with these studies is explained by the fact that patients in our study were admitted in worse clinical condition and needed emergent hematoma evacuation.

One of the limitations of the current study is that, since it is a single-center study, the sample size of bAVM-ICH is relatively small, which may have introduced selection bias. In addition, the indication for surgical evacuation of the ICH was set by the treating physician, which might also have introduced a selection bias. In addition, missing data were retrospectively collected from our hospital information system and telephone interview with the patient or the general practitioner, which can lead to recall bias, since they may remember patients' conditions wrongly at different time points.

CONCLUSION

Brain AVM patients who need surgical evacuation of an intracerebral hematoma have a more favorable outcome than surgically treated patients with spontaneous ICH at short- and long-term follow-up (6 weeks and 12 months), even after correction for confounding factors, such as younger age and less premorbid hypertension. A thorough radiologic investigation of the underlying pathology of intracerebral hematoma is mandatory to assess functional outcome after surgical evacuation. We suggest that treatment and management decisions, as well as information about the prognosis after bAVM-ICH, should not be based on results of SICH research.

ACKNOWLEDGMENTS

Elisabeth Jehli and Johannes Sarnthein developed the quality registration database of the Department of Neurosurgery in which patient data are collected prospectively.

Table 3. Case Fatality in Brain Arteriovenous Malformation–Associated Intracerebral Hemorrhage and Spontaneous Intracerebral Hemorrhage

Interval	bAVM-ICH (n = 26)	SICH* (n = 115)	OR (95% CI)	Adjusted OR† (95% CI)
6 weeks	4 (15.3)	38 (33.0)	0.37 (0.12–1.14)	0.36 (0.11–1.20)
6 months	8 (30.8)	43 (37.7)	0.73 (0.29–1.83)	0.78 (0.29–2.07)
12 months	8 (30.8)	48 (42.1)	0.61 (0.24–1.52)	0.63 (0.24–1.66)

All parameters are presented in numbers with percentages between brackets, unless otherwise stated.
bAVM-ICH, brain arteriovenous malformation–associated intracerebral hemorrhage; SICH, spontaneous intracerebral hemorrhage; OR, odds ratio; CI, confidence interval.
*1 patient lost follow-up after 6 weeks' post surgery.
†Adjust for age, side of hematoma, history of hypertension, and hyperlipidemia.

REFERENCES

1. Richard G, Ellenbogen SIA, Laligam N. *Principles of Neurological Surgery. 3rd ed.* 2012.
2. Choi JH, Mast H, Sciacca RR, et al. Clinical outcome after first and recurrent hemorrhage in patients with untreated brain arteriovenous malformation. *Stroke*. 2006;37:1243-1247.
3. van Beijnum J, Lovelock CE, Cordonnier C, et al. Outcome after spontaneous and arteriovenous malformation-related intracerebral haemorrhage: population-based studies. *Brain*. 2009;132:537-543.
4. Morgan M, Sekhon L, Rahman Z, Dandie G. Morbidity of intracranial hemorrhage in patients with cerebral arteriovenous malformation. *Stroke*. 1998;29:2001-2002.
5. Murthy SB, Merkler AE, Omran SS, et al. Outcomes after intracerebral hemorrhage from arteriovenous malformations. *Neurology*. 2017;88:1882-1888.
6. Abecassis IJ, Xu DS, Batjer HH, Bendok BR. Natural history of brain arteriovenous malformations: a systematic review. *Neurosurg Focus*. 2014;37:E7.
7. Gross BA, Ropper AE, Du R. Vascular complications of stereotactic radiosurgery for arteriovenous malformations. *Clin Neurol Neurosurg*. 2013;115:713-717.
8. Itoyama Y, Uemura S, Ushio Y, et al. Natural course of unoperated intracranial arteriovenous malformations: study of 50 cases. *J Neurosurg*. 1989;71:805-809.
9. da Costa L, Wallace MC, Ter Brugge KG, O'Kelly C, Willinsky RA, Tymianski M. The natural history and predictive features of hemorrhage from brain arteriovenous malformations. *Stroke*. 2009;40:100-105.
10. Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. *Brain*. 2001;124(Pt 10):1900-1926.
11. Spetzler RF, Kondziolka DS, Hagashida RT. *Kalani Comprehensive Management of Arteriovenous Malformations of the Brain and Spine. 1st ed.* Cambridge, United Kingdom: Cambridge University Press; 2014.
12. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. 2010;9:167-176.
13. Fogelholm R, Murros K, Rissanen A, Avikainen S. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. *J Neurol Neurosurg Psychiatry*. 2005;76:1534-1538.
14. Flaherty ML, Haverbusch M, Sekar P, et al. Long-term mortality after intracerebral hemorrhage. *Neurology*. 2006;66:1182-1186.
15. Sacco S, Marini C, Toni D, Olivieri L, Carolei A. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. *Stroke*. 2009;40:394-399.
16. Moulin S, Cordonnier C. Prognosis and outcome of intracerebral haemorrhage. *Front Neurol Neurosci*. 2015;37:182-192.
17. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2014;85:660-667.
18. Neidert MC, Lawton MT, Kim LJ, et al. International multicentre validation of the arteriovenous malformation-related intracerebral haemorrhage (AVICH) score. *J Neurol Neurosurg Psychiatry*. 2018;89:1163-1166.
19. Hartmann A, Mast H, Mohr JP, et al. Morbidity of intracranial hemorrhage in patients with cerebral arteriovenous malformation. *Stroke*. 1998;29:931-934.
20. Neidert MC, Lawton MT, Mader M, et al. The AVICH score: a novel grading system to predict clinical outcome in arteriovenous malformation-related intracerebral hemorrhage. *World Neurosurg*. 2016;92:292-297.
21. Kothari RU, Brott T, Broderick JP, et al. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke*. 1996;27:1304-1305.
22. Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology*. 2006;66:1350-1355.
23. Kader A, Young WL, Pile-Spellman J, et al. The influence of hemodynamic and anatomic factors on hemorrhage from cerebral arteriovenous malformations. *Neurosurgery*. 1994;34:801-808.
24. Spetzler RF, Hargraves RW, McCormick PW, Zabramski JM, Flom RA, Zimmerman RS. Relationship of perfusion pressure and size to risk of hemorrhage from arteriovenous malformations. *J Neurosurg*. 1992;76:918-923.

Conflict of interest statement: Wenhua Sun received funding from the China Scholarship Council to do research at the University Hospital Zurich, Switzerland.

Received 27 February 2020; accepted 22 April 2020

Citation: World Neurosurg. (2020) 139:e807-e811. https://doi.org/10.1016/j.wneu.2020.04.170

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***